DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

June 14, 2002

By Certified Mail – Return Receipt Requested
And Facsimile Transmission

CBER – 02 -013

Warning Letter

Dan F. Ausman
Chief Executive Officer
Irvine Regional Hospital and Medical Center
Tenet Health System
16200 Sand Canyon Avenue
Irvine, California 92618

Dear Mr. Ausman:

During the period of April 5, 2001, and May 31 to June 14, 2001, Allen F. Hall, an investigator with the Food and Drug Administration (FDA), conducted an inspection of the Institutional Review Board (IRB) of Irvine Regional Hospital and Medical Center. The purpose of this inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, which are published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. At the conclusion of the inspection, a Form FDA 483, List of Inspectional Observations, was issued to the IRB Chair, Dr. Lalita Pandit.

We have determined that the IRB violated regulations governing the composition, operation, and responsibilities of Institutional Review Boards as published under 21 CFR 50 and 56 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below.

1. **Failure to prepare, maintain, and follow adequate written procedures for conducting the review of research, including periodic review. [21 CFR §§ 56.108(a) and 56.115(a)(6)].**

   A. The IRB's procedures, contained in a document titled "STANDARD PROCEDURES FOR REVIEW AND APPROVAL OF RESEARCH PROTOCOLS INVOLVING HUMAN SUBJECTS," do not constitute adequate written procedures because the document does not describe in detail the following:

i. The document does not establish procedures to enable the IRB to conduct the activities described in 56.108(a), including initial and continuing review of research. Specifically, the procedures do not describe:

- How many voting members make up the IRB,
- How the IRB members are selected, and their official duties and responsibilities, including the roles of the Chair and "Ex-Officio" members;
- How controverted issues are decided;
- How the IRB will consider research proposed by IRB members:
- How the IRB will avoid conflict of interest in its reviews;
- How the IRB will review adverse reaction reports;
- How the IRB will review information distributed relating to the recruitment of subjects for studies approved by the IRB; and
- How the IRB will review proposed research and proposed consent forms for information regarding the charging of study subjects for investigational products used in a clinical trial under an IND or IDE.

ii. The procedures do not state how the IRB ensures that changes in approved research will not be initiated without IRB review and approval, and specifically do not address incorporating revisions to proposed research and for notifying the full IRB of those revisions, and how the IRB will assure that studies "approved" pending modifications are not initiated before the IRB accepts the modified documents.

B. The IRB failed to follow its written procedures for initial and continuing review. The following examples are not a complete list:

i. The IRB failed to send a "warning letter" to Dr. Kenneth M. Tokita, and later failed to terminate the study entitled [redacted] when he failed to submit the required written quarterly status reports to the IRB. Written procedures required a warning letter and study termination under these circumstances.

ii. The IRB failed to specify the frequency of progress reports in the approval notice dated [redacted] Written procedures required the IRB to specify the frequency of progress reports.

iii. The IRB failed to ensure that progress reports contained all the information required by page 6 of Appendix B to the written procedures, to determine if a study should continue, be modified, or terminated. For example, the minutes of 11/9/00 document that the IRB accepted a progress report for the study entitled [redacted] that reported only the number of subjects enrolled, withdrawn, and explanted, while omitting information required in Appendix B.

2. **Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one nonscientific member. [21 CFR § 56.108(c)].**

A. IRB meeting minutes for 4/27/00 document the following two studies were approved by mail ballot instead of at a regularly convened meeting:

[redacted]

B. The IRB did not establish a quorum at:

i. The 1/25/01 meeting, when the IRB approved the new research protocol [redacted] There were only three of nine voting members present at the meeting.

ii. The 11/9/00 meeting, when the IRB conducted continuing review of the study [redacted] There were only two of nine voting members present at this meeting.

iii. The 7/13/00 meeting, when continuing review of studies and amendments to protocols were presented, discussed, and approved. The minutes list only three voting IRB members present, and three "Ex-Officio" members. The IRB's list of members does not include "Ex-Officio" members nor do the written procedures describe the selection, official duties, or voting rights of "Ex-Officio" members.

C. The IRB did not have a nonscientific member present during the meetings held on 1/25/01 and 11/9/00 when new research proposals and continuing review of studies were presented to and approved by the IRB.

3. **Failure to conduct continuing review of research at intervals appropriate to the degree of risk. [21 CFR § 56.109(f)].**

   Due to the degree of risk associated with the study protocol entitled _____ the IRB concluded that continuing review should be done on a quarterly basis for the first year and bi-annually thereafter. There is no documentation of either quarterly or bi-annual review of this study being conducted by the IRB.

4. **Failure to ensure that research is reviewed free from conflict of interest. [21 CFR § 56.107(e)].**

   IRB members did not always exclude themselves from deliberation and voting on projects in which they were involved. For example, several IRB committee members were directly involved in the study entitled _____ However, the meeting minutes for 4/27/00 document that those IRB members were present and that the study was unanimously approved by the IRB. There is no indication the IRB members involved in the study excluded themselves from voting on the project.

5. **Failure to fulfill requirements for expedited review. [21 CFR § 56.110(b)(1)].**

   An IRB may review certain research using an expedited review procedure only if the research involves no more than minimal risk to subjects. Meeting minutes for 7/13/00 document the IRB Chair inappropriately used the expedited review process to approve the participation of a 6-year old child in the study protocol entitled _____

   This protocol involved more than minimal risk and the investigator's request was to waive certain protocol requirements. Therefore, the request should have been brought before the full IRB for review.

6. **Failure to fulfill membership requirements. [21 CFR § 56.107(f)].**

   The IRB allowed a non-member to vote on a proposed research project. The IRB requested Dr. Malin Dollinger, a non-IRB member, to vote (via mail ballot) on the proposed research protocol entitled _____ The request letter dated November 22, 1999 states "Please review the enclosed protocol before casting your vote."

7. **Failure to exercise authority to review and approve, require modification in, or disapprove all research activities covered by the regulations. [21 CFR § 56.109(a)].**

   A. IRB practices are inadequate to assure that new studies "approved" pending modifications are not initiated or that ongoing studies are not allowed to continue without submission and approval by the IRB of modified documents.

   B. The IRB does not review the proposed research to assess whether the study involves charging subjects for investigational products under FDA jurisdiction. For example, the IRB approved the study entitled [redacted] in which the clinical investigator was charging subjects $15,000 to participate in the research. The study was submitted to FDA under an IND and cost recovery was not authorized.

8. **Failure to determine and assure that risks to subjects are minimized. [21 CFR § 56.111(a)(1) and (6)].**

   A. The IRB approved the study protocol entitled [redacted] even though the protocol lacked the following: specific study objectives and end-points, specific inclusion and exclusion criteria (such as measurable or evaluable disease at the time of enrollment), stated parameters for subject management and follow-up (such as how subjects will be monitored for adverse events and disease status. [redacted], clear stopping rules, and clear toxicity grading criteria.

   This study was submitted to FDA under an IND and was rejected for the aforementioned deficiencies. However, the IRB approved this study and the associated informed consent document that lacks most of the major required elements, as described in item 9A, below.

   B. The IRB reviewed and approved the study entitled [redacted] yet the study procedures were not consistent with sound research design and unnecessarily exposed subjects to risk. This study enrolled 16 patients resulting in four reported deaths, [redacted] This study, and all other [redacted] studies submitted by Dr. Tokita, includes the [redacted]

C. All of the IRB-approved [redacted] " study protocols lack specific donor suitability requirements. The protocols refer to meeting "Red Cross" standards, however, the questionnaire for the leukapheresis consent form used for all the studies does not question the donor for high-risk behavior or possible exposure to hepatitis or malaria.

[redacted]

D. During the meeting of September 28, 2000, the IRB discussed a reported adverse reaction following a [redacted] that resulted in the subject's death. The meeting minutes list six "recommendations" for adjustments to the protocol, including the following:

[redacted]

These "recommendations" are actually important modifications of the clinical study, and a condition of continuing approval for the study. However, there is no documentation in subsequent IRB meeting minutes that confirm that the required formal report by Dr. Tokita and the protocol modifications were made.

E. The IRB lacks a process for determining if a research activity involves an investigational product subject to FDA regulation.

9. **Failure to require that information given to subjects as part of informed consent is in accordance with the provisions of 21 CFR §§ 50.20, 50.25, and 50.27. [21 CFR § 56.109(b) and (c)].**

The IRB approved consent forms that did not meet the requirements of 21 CFR §§ 50.20, 50.25 and 50.27. The consent forms submitted by Dr. Tokita with the protocols entitled ", [redacted] " are representative samples.

A. The consent forms lacked the following elements required by 21 CFR §§ 50.25 and 50.27(b)(1) (not a complete list):

i. A statement concerning the expected duration of participation in the study.

ii. The various procedures subjects would undergo, such as x-rays, MRIs, scans, and multiple venipunctures.

iii. A description of the reasonably foreseeable risks and discomforts associated with the procedures, including the risk of diseases ; and those associated with chemotherapy.

iv. A disclosure of appropriate alternative procedures or therapies that might benefit the subject.

v. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.

vi. A statement indicating that the procedure may include risks to the embryo or fetus if the subject became pregnant during the study.

vii. A statement regarding additional costs to the subject that may result from participation in the research.

viii. A statement of the number of subjects involved in the study.

B. The IRB approved consent forms that contain technical language, medical terminology, and important concepts that as currently worded are not readily understandable by a layperson, thereby limiting a subject's ability in making a true informed consent. 21 CFR § 50.20 requires that information in consent forms be written in language understandable to the subject or representative.

C. The consent forms inaccurately describe benefits that could be reasonably expected from the research. Examples include but are not limited to the following. "It has been Easy and Relatively Safe;" "...to confirm a very exciting and promising treatment;" "... simple modifications to the Project that have been proposed..." "Follow up work at other centers...from a Donor...has been very encouraging...;" and "Hopefully Cure my Cancer."

D. The consent forms contain exculpatory language that waives or appears to waive the subject's legal rights, and releases or appears to release the clinical investigator and the institution from liability, despite the prohibition against such exculpatory language contained in 21 CFR § 50.20.

Examples include but are not limited to the following. "I realize the experimental nature of this project and agree there is no way to anticipate problems, and therefore hold none of the physicians or hospital liable for any problems that arise, as long as all their best efforts are expended in my behalf."

E. The consent forms state "... copy of this form will be made available upon request." 21 CFR § 50.27(a) requires that a copy be given to the subject.

10. **Failure to prepare sufficiently detailed meeting minutes. [21 CFR Part § 56.115(a)(2)].**

The minutes of the IRB meetings are not in sufficient detail to show all actions taken by the IRB; the vote on those actions, including the number voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the controverted issues and their resolution.

This letter is not intended to be an all-inclusive list of deficiencies.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures, with your response. Any plans of action must include projected completion dates for each action to be accomplished.

Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions include FDA prohibiting the approval by your IRB of new studies that are subject to Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to 21 CFR Parts 50 and 56; terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Robert L. Wesley
Division of Inspections and Surveillance (HFM-664)
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Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
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Telephone:(301) 827-1948

We request that you send a copy of your response to the FDA office listed below.

Sincerely,

Steven A. Maslello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc:

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